UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,393	07/30/2001	Ira Pastan	15280-3721US	5265

7590 09/13/2005

KLARQUIST SPARKMAN, LLP
ONE WORLD TRADE CENTER SUITE 1600
121 SW SALMON STREET
PORTLAND, OR 97204-2988

EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,393	PASTAN ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14-18 and 52-60* is/are pending in the application.

4a) Of the above claim(s) *9-12,16 and 58-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,14,15,17,18 and 53-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/06/02;07/16/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Group I, Claims 1-8, 14-15, 17, directed to the polypeptide of SEQ ID NO:1, a fragment thereof, and a method for reducing the growth of malignant cells using the claimed polypeptide, or fragment thereof, in Papers of 04/25/05 and 08/04/05 is acknowledged and entered.

Applicant cancels claims 13, 19-51, amends claim 18, and adds new claims 52-60.

In the response to the non-compliant amendment of 08/04/05, Applicant asserts that claim 52 was present in the amendment of 04/25/05 and 08/04/05.

The arguments are not found to be persuasive, because claim 52 in the amendment of 04/25/05 and 08/04/05, drawn to the polypeptide of claim 1, comprising SEQ ID NO:1, is a new claim, whereas claim 52 submitted on 07/30/01 is an original claim, drawn to a kit comprising a nucleic acid sequence that hybridizes to a portion of the PAGE-4 gene.

Accordingly, new claims 52-59 are renumbered as claims 53-60, according to rule 26.

Claims 1-12, 14-18, 52-60 are pending in the instant application and Claims 9-12, 16, 52, 58-60 have been withdrawn from further consideration by the Examiner under 37 CFR 1.142(b) as being drawn to non-elected invention.

Claim 18 was rejoined with claims 1-8, 14-15, 17, because claim 18 has been amended to be dependent to claim 4, and drawn to a method for inhibiting growth of a malignant cell, using the polypeptide of claim 4.

Accordingly, Claims 1-8, 14-15, 17-18, and new claims 53-57 are currently under prosecution.

The traversal is on the following ground(s):

Applicant recites Chapter 10, Example 39, Protein and its encoding DNA, of the PCT guidelines, and argues that Group I (polypeptides and their use to treat tumors) should be rejoined with group II (polynucleotides), because the protein makes a contribution over the prior art, the protein and DNA share a corresponding technical feature, and the claims have unity.

Applicant's arguments have been considered but are found not to be persuasive for the following reasons:

It is noted that the independent claims 1 and 9 of **the claimed invention are drawn to a genus of polynucleotides encoding a "genus" of polypeptides**, whereas **Example 39 represents a single species of a protein and a genus of nucleic acids**, which encode the protein.

Example 39 specifically indicates that unity of invention between the protein and its corresponding encoding DNA sequetwe requires that protein and the DNA sequence exhibit corresponding special technical features.

The nucleotide sequences encoding the polypeptides of group II, do not exhibit corresponding special technical feature with the polypeptides "comprising" 8 to 11 amino acids, or "is" 9 to 11 amino acids of SEQ ID NO:1 claimed in group I, as required by the PCT Administration Instructions, Example 17.

That is, the structure of a genus of the claimed polypeptides "comprising" 8 to 11 contiguous amino acids of SEQ ID NO:1, i.e., unknown sequences attached to a fragment of 8-11 amino acids of SEQ ID NO:1, is not disclosed, nor predicted, therefore, the polynucleotides of group II could not share the same technical feature as those unknown polypeptides "comprising" 8 to 11 contiguous amino acids, or "is" 9 to 11 contiguous amino acids of SEQ ID NO:1.

Further, the full length polynucleotides of group II do not encode the claimed peptide "consisting" of 8 to 11 or 9 to 10 contiguous amino acids of SEQ ID NO:1 of group I.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 1-8, 14-15, 17-18, 53-57 are examined in the instant application.

New claims 58-60 are withdrawn from consideration as being drawn to non-elected invention, because new claims 58-60, drawn to a polynucleotide, and a vector comprising said polynucleotide, belong to group II, for reasons set forth above.

OBJECTION

The amendment of the drawing of 09/02/04 is objected to, because figure 5 is not a sequence, whereas in the original application of 07/30/2001, figure 5 is a sequence.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 1-8, 14-15, 17-18, 53, 55, 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8, 14-15, 17-18, 53, 55, 57 are indefinite for the use of the language "the peptide" in claim 1, which lacks antecedent basis. Amendment of claim 1, for example, to substitute the term "polypeptide" for the term "peptide" would obviate the rejection.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 1-8, 14-15, 17-18, 54-57 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 1-8, 14-15, 17-18, 54-57 are drawn to:

1) an isolated polypeptide "comprising" or "consisting essentially of" or consisting of 8 to 11 or 9 to 10 amino acids of SEQ ID NO:1, wherein "the peptide binds major histocompatibility complex (MHC) I, or HLA-A1, -A2.1, -A3.2, -A4.1, -A11.2 ". An isolated polypeptide of claim 1, wherein the polypeptide "is" 9 to 10 amino acids in length. Said polypeptide of claim 3 or 54 could be conjugated to a lipid (claims 1, 3, 5, 6, 54-57).

2) "An immunogenic composition" comprising a polypeptide "comprising" or "consisting essentially of" 8 to 11 amino acids of SEQ ID NO:1, wherein "the peptide binds major histocompatibility complex (MHC) I. Said polypeptide of claim 2 or 4 could further comprise two or more of a stabilizing agent, a micelle-forming agent, and an oil (claims 2, 4, 7-8).

3) A method for inhibiting the growth of a malignant cell expressing "PAGE-4", comprising culturing CTLs or CTL precursor cells with the polypeptide of claim 1, and contacting the malignant cell with activated CTLs or CTLs matured from the CTL precursor (claim 14).

4) A method for inhibiting the growth of a malignant cell expressing "PAGE-4", in a mammal with a malignancy comprising "PAGE-4" expressing cells, comprising culturing CTLs or CTL precursor cells with the polypeptide of claim 3, and introducing into the mammal the activated CTLs or CTLs precursors (claim 15).

5) A method for inhibiting the growth of a malignant cell expressing "PAGE-4", in a mammal with a malignancy comprising "PAGE-4" expressing cells, comprising administering the immunogenic composition of claim 2 or 4 (claims 17-18).

The specification discloses that "an immunogenic composition" refers to a composition comprising a PAGE-4 protein or a peptide derived from a PAGE-4 protein, when bound to a MHC I molecule, induces a measurable CTL response against cells expressing PAGE-4 protein (p.8, lines 30-34). Based on the above definition, "An immunogenic composition" comprising a polypeptide comprising or consisting essentially of 8 to 11 amino acids of SEQ ID NO:1, wherein the peptide binds major

histocompatibility complex (MHC) I encompasses peptides of SEQ ID NO:1, wherein said peptides could induces a measurable CTL responses.

It is noted that not any peptides of a protein are able to bind to a particular MHC molecule, and elicit T cell response. Roitt I et al, 1998, Immunology, 4th ed, Mosby, London, page 7.9, teach that only a minority of peptide fragments from a protein antigen are able to bind to a particular MHC molecule.

However, the structure of which peptides of 8-11 or 9-10 amino acids of SEQ ID NO:1, that bind to MHC(I) or that could elicit CTL response is not described in the specification.

It is further noted that due to the language "consisting essentially of", or "is" which is reasonably interpreted to be the same as the open language "comprising", **an isolated polypeptide "comprising" or "consisting essentially of" 8 to 11 or "is" 9 to 10 amino acids of SEQ ID NO:1 encompasses unknown sequences that are attached to peptides of 8 to 11 or 9 to 10 amino acids of SEQ ID NO:1**.

In addition, based on the following disclosure concerning the "PAGE-4 protein" in the specification, **the language "PAGE-4" in claims 14, 15, 17-18 encompasses variants of the PAGE-4 of SEQ ID NO:1, with unknown structure**.

The specification discloses that with respect to immunogenic compositions comprising a PAGE-4 protein, "PAGE-4 protein" further refers to variation of to wild type PAGE-4, having conservative substitution or deletions or insertions of one or more amino acids, provided the variations do not alter by more than 20% the ability of the

protein to activate cytotoxic T lymphocytes against cells expressing the wild type PAGE-4 protein (p. 7, lines 21-26).

There is, however, no teaching in the specification of any common structural features of the claimed variants PAGE-4, coupled with a correlation between function and structure, nor of the claimed peptides that bind major histocompatibility complex (MHC) I, or that could induce CTL response.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, " requires a precise definition, such as by structure, formula, [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus,

> visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that □naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that □the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of the claimed polypeptides that bind major histocompatibility complex (MHC) I, or that could induce CTL response, or of variants PAGE-4, as shown in the example of Lilly by structurally describing a representative number of the claimed polypeptides or PAGE-4, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, as shown in the example of Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the claimed polypeptides that bind major histocompatibility complex (MHC) I, or that could induce CTL response, or variants PAGE-4, in a manner that satisfies either the standards as shown in the example of Lilly or Enzo. The specification does not provide the complete structure of any polypeptide that binds to MHCI or that could elicit T cell response, or any PAGE-4, other than SEQ ID NO:1, nor does the specification provide any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single polypeptide of SEQ ID NO:1, this

does not provide a description of the claimed polypeptides that bind major histocompatibility complex (MHC) I, or that could induce CTL response, or PAGE-4, that would satisfy the standard as shown in the example of Enzo.

The specification also fails to describe the claimed polypeptides that bind major histocompatibility complex (MHC) I, or that could induce CTL response, or PAGE-4 by the example in Lilly. The specification describes only a single polypeptide of SEQ ID NO:1 Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the claimed polypeptides or PAGE-4, that is required to practice the claimed invention.

In addition, since the specification fails to adequately describe the polypeptide and PAGE-4 product for use in the claimed methods of claims 14-15, 17-18, it also fails to adequately describe the claimed methods.

REJECTION UNDER 35 USC 101, UTILITY

35 U.S.C. 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1-8, 14-15, 17-18, 53-57 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial asserted utility or a well established utility.

Claims 1-8, 14-15, 17-18, 53-57 are drawn to:

1) an isolated polypeptide comprising SEQ ID NO:1 (claims 1, 53). The polypeptide of claim 1, wherein the polypeptide "is" 9 to 10 amino acids in length (claim 54).

2) an isolated polypeptide "comprising" or "consisting essentially of" or consisting of 8 to 11 amino acids of SEQ ID NO:1, wherein "the peptide binds major histocompatibility complex (MHC) I, or HLA-A1, -A2.1, -A3.2, -A4.1, -A11.2 ". Said polypeptide of claim 3 or 54 could be conjugated to a lipid (claims 1, 3, 5, 6, 53, 57).

3) "An immunogenic composition" comprising a polypeptide "comprising" or "consisting essentially of" 8 to 11 amino acids of SEQ ID NO:1, wherein "the peptide binds major histocompatibility complex (MHC) I. Said polypeptide of claim 2 or 4 could further comprise two or more of a stabilizing agent, a micelle-forming agent, and an oil (claims 2, 4, 7-8).

4) A method for inhibiting the growth of a malignant cell expressing PAGE-4, comprising culturing CTLs or CTL precursor cells with the polypeptide of claim 1, and contacting the malignant cell with activated CTLs or CTLs matured from the CTL precursor (claim 14).

5) A method for inhibiting the growth of a malignant cell expressing PAGE-4, in a mammal with a malignancy comprising PAGE-4 expressing cells, comprising culturing

CTLs or CTL precursor cells with the polypeptide of claim 3, and introducing into the mammal the activated CTLs or CTLs precursors (claim 15).

6) A method for inhibiting the growth of a malignant cell expressing "PAGE-4", in a mammal with a malignancy comprising "PAGE-4" expressing cells, comprising administering the immunogenic composition of claim 2 or 4(claims 17-18).

The specification discloses that the polynucleotide encoding SEQ ID NO:1 underexpressed in prostate cancer as compared to normal prostate (figure 4 and p.16), and is overexpressed in uterine cancer as compared to normal uterine (Figure 2B and p.16).

The specification further discloses that the predicted PAGE-4 polypeptide of SEQ ID NO:1 has similarity with some amino acids of MAGE5, GAGE and other PAGEs (figure 1).

The specification contemplates determining motifs or peptides that that binds to MHC I, using computer program known in the art, and that given some similarity with MAGE proteins, it is expected to use the procedure for MAGE-2 or MAGE-3 to find and test potential CTL epitopes for PAGE-4 for use in vaccines and ex vivo uses (p.20-25, especially p.22, lines 24-28, p. 24-25).

The specification discloses that the peptide of SEQ ID NO:16 could be used for generating antibodies. However, there is no disclosure that said peptide binds to MHC I, nor is there disclosure that said peptide activates the cytotoxic T cells (CTLs). It is noted that a peptide binds to B cells for producing antibodies.

One cannot determine that SEQ ID NO:1 could be used for diagnosis or treatment of cancers, as contemplated in the specification, and further experimentation is required to determine what the use is for the claimed polypeptides of SEQ ID NO:1 or its fragments of 8 to 10 or 11 amino acids.

One cannot determine that SEQ ID NO:1 or its fragment could be used for diagnosis of cancers, because, although the polynucleotide encoding SEQ ID NO:1 is differentially expressed in prostate and uterine cancers as compared to normal controls, **one cannot predict that the encoded SEQ ID NO:1 is also differentially expressed in prostate and uterine cancers as compared to normal controls, in view that protein levels cannot be predictably correlated with steady-state mRNA levels or alterations in mRNA levels.** For instance, Brennan et al (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) teach that high levels of the mRNA for TNF alpha were produced in synovial cells, but that levels of the TNF alpha protein were undetectable. Further, Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. Eriksson et al (Diabetologia, 1992, vol. 35, pp. 143-147) teach that no correlation was observed between the level of mRNA transcript from the insulin-responsive glucose transporter gene and the protein encoded thereby. Hell et al (Laboratory Investigation, 1995, Vol. 73, pp. 492-496) teach that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. Guo et al (Journal of Pharmacology and

Experimental Therapeutics, 2002, vol. 300, pp. 206-212) teach that Oatp2 mRNA levels did not show a correlation with Oatp2 protein levels, suggesting that regulation of the Oatp2 protein occurs at both the transcriptional and post-ranslational level. These references serve to demonstrate that levels of polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression. In view of the teaching in the art, one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification.

Further, **one cannot determine that SEQ ID NO:1 or its fragments could be used for producing specific CTLs effective for cancer treatment, because 1) Cancer treatment is unpredictable, and 2) one cannot predict that SEQ ID NO:1 contains TCLs epitopes that are adequately immunogenic and exposed in sufficient quantities on surface of malignant cells in vivo, such that CTLs could recognize and lyse said malignant cells**. Further experimentation is required to determine what the use is for the claimed polypeptides of SEQ ID NO:1 or its fragments of 8 to 10 or 11 amino acids that binds MHC I.

It is well known in the art that cancer treatment is unpredictable, and that the problem with tumor tolerance and the loss of surface Class I MHC is well known. For example, Smith RT, 1994, Clin Immunol, 41(4): 841-849, teaches that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches that many tumors progressively lose

MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limits the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specfic antigen in the necessary MHC context (p.484). Similarly, Boon (Adv Can Res, 1992, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). In addition, Boon teaches even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph).

Further, the goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3) recognizes the lack of predictability of the nature of the art when she

states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1).

Further, there is insufficient guidance regarding the parameters and sequence of peptides, which correlate with the ability to stimulate and generate specific CTLs with high affinity, that recongnize SEQ ID NO:1 on in vivo malignant cell surface, and kill said malignant cells.

Although SEQ ID NO:1 has some amino acid similarity with MAGE proteins, there is no teaching in the specification whether there exists any peptide of SEQ ID NO:1, which is the same as the peptides in MAGE proteins, and which could elicit CTLs response with anti-tumor activity. Further, it is noted that although several peptides of melanoma associated antigens have been identified as recognized by CTL in vitro, and peptides from MAGE-A1 and MAGE-A3 have been tested for their ability to induce anti-melanoma immune response in vivo, so far only one of the peptides, peptide EVDPIGHLY of MAGE-A3, has limited anti-tumor activity, indicating their low immunogenicity (Kirkin et al, 1998, APMIS, 106 : 665-679, especially p.666, second column, second paragraph, last 6 lines). In view of the extreme limited number of peptide (i.e. only one identified so far) from MAGE proteins that could induce CTLs having in vivo anti-tumor activity, one cannot predict that SEQ ID NO:1 contains peptides that could elicit specific CTLs with high affinity, that recognize and kill in vivo malignant cells.

Further, even CTLs, that could be activated by SEQ ID NO:1 protein, or fragments thereof, could be produced, one cannot predict whether said CTLs would recognize and lyse malignant cells expressing SEQ ID NO:1 in vivo, due the unpredictability of sufficient quantity of the protein expressed on the surface of the malignant cells. This possible problem with insufficient quantity of SEQ ID NO:1 expressed on malignant cells could further be exacerbated, in view that cancer cells could downregulate the expression of tumor antigens, and thus reducing the amount of the antigens presented, and consequently the possibility of being recognized and lysed by CTLs, and further in view of the well-known cancer tolerance phenomena. For example, White et al, 2001, Ann Rev Med, 52: 125-145, teach that antigen internalization or downregulation can cause repeat dosing to be unsuccessful due to the disappearance of the antibody target (p.126, paragraph before last). Smith RT, 1994, Clin Immunol, 41(4): 841-849, teaches that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches that many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limits the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specfic antigen in the necessary MHC context (p.484). Similarly, Boon (Adv Can Res, 1992, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent

immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2).

Moreover, based on sequence similarity with MAGE proteins, one cannot determine that SEQ ID NO:1 has the same properties and characteristics of MAGE proteins. Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Similarly, Bork et al, Genome Research, vol. 10 (2000), pp. 398-400, teach the pitfalls associated with comparative sequence analysis for predicting protein function and specifically states that conclusions from comparison analysis are often stretched with regard to protein products and specifically cites that most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality. The teaching of Scott et al, Nature Genetics, vol. 21 (April 1999), pp. 440-443, further confirm the teaching of Bork, wherein Scott et al teach an example of misidentification of the function of a protein based on homology alone, and conclude that it is important to confirm the function of a newly identified gene products even when the database reveal significant homology to proteins of known function.

Neither the specification nor any art of record teaches what the polypeptide is, what it does. The specification does not teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease or teach which fragments might be active would function as claimed.

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 1-8, 14-15, 17-18, 53-57 are rejected under 35 U.S.C. 112, first paragraph.

A. Specifically, since the claimed invention is not supported by specific, substantial utility or a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

B. If Applicant could overcome the above 101, and 112, first paragraph rejections, claims 1-4, 6-8, 14-15, 17-18, 54 are still rejected under 35 USC 112, first paragraph, because claims 1-4, 6-8, 14-15, 17-18, 54 lack enablement for a polypeptide "comprising", or "consisting essentially" of 8 to 11, or "is" 9 to 10 contiguous amino acids of SEQ ID NO:1, wherein the polypeptide binds MHC I, and a method of inhibiting growth of a malignant cell, using said polypeptide.

It is noted that the language "consisting essentially of", or "is" could be reasonably interpreted to be the same as the open language "comprising".

Thus an isolated polypeptide "comprising" or "consisting essentially of" 8 to 11 amino acids of SEQ ID NO:1, wherein "the peptide binds major histocompatibility complex (MHC) I", encompasses unknown sequences that are attached to peptides of 8 to 11 amino acids of SEQ ID NO:1, wherein said peptides are of unknown structure, and wherein said peptides bind major histocompatibility complex (MHC) I.

Similarly, a polypeptide of claim 1, which "is" 9 to 10 amino acids in length, encompasses sequences of unknown structure that are attached to 9 to 10 amino acid fragment of SEQ ID NO:1.

Applicant has not taught how to make the claimed numerous sequences comprising 8 to 10 or 9 to 10 amino acids of SEQ ID NO:1, that would be reasonably expected to have the same properties as SEQ ID NO:1, and to be recognized by CTLs specific for SEQ ID NO:1. For example, Applicant has not taught what the structure is for the sequences attached to the defined fragment.

Further, one could not predict whether that the claimed sequences would have the same properties or three dimensional structure as that of SEQ ID NO:1, and consequently whether the specific CTLs epitopes would be exposed on the malignant cell surface such that CTLs specific for SEQ ID NO:1 would recognize the claimed sequences, in view of teaching in the art that protein chemistry is unpredictable, and that even a single amino acid substitution or what appear to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics or conformation of a protein, as taught by Bowie et al, supra.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

C. If Applicant could overcome the above 112, first paragraph, and even if the claimed polypeptides could be used for inhibiting growth of malignant cells, claims 14-15, 17-18 are still rejected under 112, first paragraph, because Claims 14-15, 17-18 encompasses a method for inhibiting growth of a malignant cell expressing "variants" of the PAGE-4 of SEQ ID NO:1.

It is noted that "PAGE-4" encompasses variants of SEQ ID NO:4, with unknown structure, in view of the disclosure in the specification on page 7, lines 21-26 that PAGE-4 protein refers to variation of wild type PAGE-4.

Applicant has not taught how to make the PAGE-4 variants for use in the claimed method, such that they have the same properties as that of SEQ ID NO:1, and could be recognized by CTLs specific for SEQ ID NO:1.

Even if SEQ ID NO:1 could produce specific CTLs with high affinity, One cannot predict that the PAGE-4 variants have similar 3-dimensional structure as that of SEQ ID NO:1, such that the epitopes to be recognized by CTLs specific for SEQ ID NO:1 remain exposed on cell surface. It is noted that 3-dimensional structure of a protein is determined by the amino acid composition. Bowie et al (Science, 1990, 247: 1306-1310, especially columns 1-2, p.1306) teach that the ability of proteins to fold into unique three-dimensional structures depends on the amino acid composition of the protein, and that certain positions in the sequence are critical to the three dimensional structure/function relationship. Thus, based on the teaching in the art, one cannot predict what the conformation of PAGE-4 variants is, wherein said conformation is of significant importance for binding to CTLs specific for SEQ ID NO:1. One cannot predict what the conformation of the polypeptide variants would be, such that the epitopes would be recognized by the CTLs specific for SEQ ID NO:1.

The claimed PAGE-4 variants however could have any deletion or addition or substitution at any amino acids. Applicant has not taught how to make the claimed variants such that the variations do not alter the ability of the protein to activate cytotoxic T lymphocytes against cells expressing SEQ ID NO:1, and it would be undue experimentation for one of skill in the art to screen for such variants.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

D. If Applicant could overcome the above 112, first paragraph, and even if the claimed polypeptide is differentially expressed in prostate and uterine

cancers, and could be used for inhibiting growth of uterine cancer, claims 14-15, 17-18 are still rejected under 112, first paragraph, because Claims 14-15, 17-18 encompass a method for inhibiting growth of "any malignant cell" expressing SEQ ID NO:1.

It is noted that the specification discloses that **the polynucleotide encoding SEQ ID NO:1 although differentially expressed in prostate and uterine cancers, but is not found in ovarian cancer** (p.16, lines 14-16).

One cannot extrapolate the teaching in the specification to the scope of the claims, because other than prostate and uterine cancers, one cannot predict whether any other cancers also differentially expressed SEQ ID NO:1, in view of the teaching in the specification that the polynucleotide encoding SEQ ID NO:1 is not found in ovarian cancers, and further in view that different cancers have different etiology and characteristics. For example, Montesano, R et al,1996, Intl J Cancer, 69(3): 225-235, teach that two different forms of esophagus cancer, squamous cell carcinoma (SCC) and adenocarcinoma (ADC) have different etiological and pathological characteristics, and that a comparison of p53 mutations in these two cancers shows that said mutations differ by their types, frequencies, distribution along the gene and impact on p53 protein structure (p.231, second column, first paragraph). Similarly, Burmer, GC et al, 1991, Environmental Health perspectives, 93: 27-31, teach that in contrast to sporadic colon carcinomas, mutations in c-Ki-ras are infrequently observed in carcinomas or areas of high-grade dysplasia in patients with chronic ulcerative colitis, and that differences in the frequency, and spectrum of mutations observed in sporadic colon carcinoma and

pancreatic carcinoma suggest that a different class of carcinogens may be involved in the initiation of these two tumors (p.27, second column, last paragraph, bridging p.28). Busken, C et al, Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No:850, teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract).

Thus based on the teaching in the art and in the specification, one cannot predict that SEQ ID NO:1 is overexpressed in any malignant tissues as compared to normal corresponding control tissues, such that they could be killed by CTLs specific for SEQ ID NO:1.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 102(e)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2, 53, 55 are rejected under 35 U.S.C. 102(e) as being anticipated by US 20040248256A1.

Claims 1-2, 53, 55 are drawn to:

1) An isolated polypeptide comprising SEQ ID NO:1 (claims 1, 53).

2) An immunogenic composition comprising the polypeptide of claim 1 and a pharmaceutical acceptable carrier (claim 2).

3) The polypeptide of claim 1, wherein the polypeptide "is" 9 to 10 amino acids in length (claim 55).

It is noted that the specification discloses that "an immunogenic composition" refers to a composition comprising a PAGE-4 protein (p.8, lines 30-34).

It is further noted that the language "is" is interpreted as having the same meaning as the open language "comprises".

US 20040248256A1 teaches a protein of SEQ ID NO:2 having 102 amino acids in length (paragraph 0045), and a composition comprising SEQ ID NO:2 in a pharmaceutically acceptable carrier (para 2132).

The parent application 60/084564, filed on 05/07/1998, also discloses SEQ ID NO:2 (p.3, lines 8). The parent application 60/084564 further teaches a composition comprising the disclosed protein in a pharmaceutically acceptable carrier (p.17, lines 6-7).

Under MPSRCH sequence similarity search, SEQ ID NO:2 is 100% similar to the claimed SEQ ID NO:1, throughout the whole length of SEQ ID NO:2, from amino acid 1 to 102 (MPSRCH search report, 2005, us-09-763-393-1.rapb, page 2).

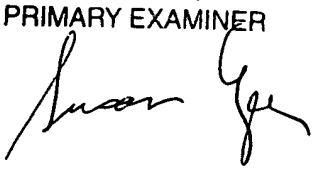
All the limitations are met.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER



MINH TAM DAVIS

August 26, 2005